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Package Insert of Enalapril Maleate and Hydrochlorothiazide Tablets (I)

Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]

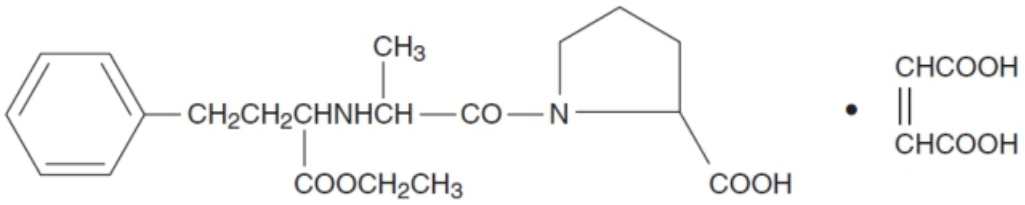
Generic Name: Enalapril Maleate and Hydrochlorothiazide Tablets (I)
Chinese Pinyin: Yinapuli Qinglüsaiqin Pian (I)

[Active Ingredients]

This product combines an angiotensin converting enzyme inhibitor, enalapril maleate, and a diuretic, hydrochlorothiazide.

Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

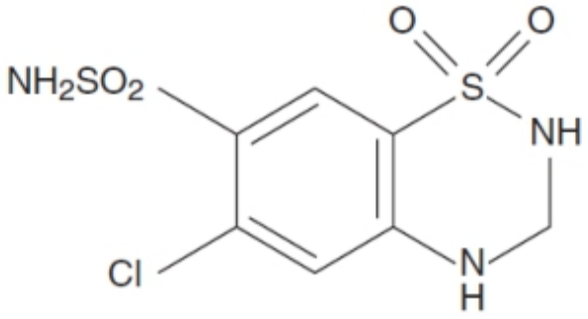
Chemical Name of the API: (S)-1-[N-[1-(ethoxycarbonyl)- 3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1)
Structural Formula:



Molecular Formula: $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$
Molecular Weight: 346.3

Hydrochlorothiazide is a diuretic agent.

Chemical Name of the API: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Structural Formula:



Empirical formula is $C_7H_8ClN_3O_4S_2$
Molecular Weight: 297.74
JiuBaoKe is available in the tablet combination of enalapril maleate with hydrochlorothiazide: JiuBaoKe containing 10 mg enalapril maleate and 6.25 mg hydrochlorothiazide.

[Inactive Ingredient]
Sodium Bicarbonate, Starch, Lactose, Cellulose Microcrystalline, Pregelatinized starch, Carboxymethyl starch Sodium, Povidone, Purified Water, Magnesium Stearate, Talc Powder, Spectrablend Pink.

[Properties]
This product is a film-coated tablets and the core inside is white.

[Indications]
JiuBaoKe is indicated for the treatment of hypertension.

This fixed dose combination is not indicated for initial treatment
In using JiuBaoKe, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril does not have a similar risk
In considering use of JiuBaoKe, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

[Strength]
10 mg enalapril maleate and 6.25 mg hydrochlorothiazide.

[Dosage and Administration]

Oral administration, 1~2 tablet at a time, once daily; or follow doctor's instruction.

[Adverse Reactions]
Common: Dizziness, Headache, Fatigue, Cough, usually mild and short.
Less Common: Muscle spasm, Nausea, Weak, Postural change discomfort, Diarrhea, Impotence.
Rare: Syncope, Hypotension, Orthostatic hypotension, Palpitation, Tachycardia; Vomiting, Ingestion, Dry mouth, Constipation, Insomnia, Nervous, Paresthesia; Rash, Itching; Angioedema, might be fatal if occur at neck, patients should stop the medication immediately. The treatment is subcutaneous adrenaline injection 0.3 ~ 0.5 ml.

[Contraindications]
Allergic to any component of this product and previous treatment of other angiotensin-converting enzyme inhibitors cause angioedema, patients with hereditary and idiopathic angioedema history should be banned from this product; due to the hydrochlorothiazide component, this product is contraindicated in patients with nocturia or allergies to sulfa drugs; this product is contraindicated in patients with severe renal insufficiency.

[Precautions]
(1) For patients with insufficient blood supply to the heart or cardiovascular disease, or patients with severe hypovolemia due to strong diuretic should be used with caution to prevent excessive hypotension, myocardial infarction, and cerebrovascular accidents.
(2) Patients with double and unilateral renal artery stenosis may have increased hematuria and serum creatinine.
(3) Patients with liver dysfunction or progressive liver disease should be used with caution.
(4) Patients with diabetes, gout, and systemic lupus erythematosus should be used with caution.
(5) Patients who are deficient in bodily fluids or sodium salts due to use diuretics in advance are prone to have symptomatic hypotension. For these patients, diuretics should be discontinued for 2-3 days when starting to use this product.
(6) This product is not for initial treatment for patients.
(7) athletes should use with caution.

[Use in Pregnant and Lactation]
This product can pass through the placenta. In the middle and late term of pregnancy, enalapril is reported to cause neonatal hypotension, renal failure, skull dysplasia, or death. Premature oligohydramnios also occurs, so pregnant women are banned from this product. This product can be excreted into milk, so is not recommended for lactating women.

[Pediatric Use]
Safety and effectiveness in pediatric patients have not been established.

[Geriatric Use]
In the clinical study of enalapril and hydrochlorothiazide, the efficacy and tolerability of elderly and young hypertension patients are similar, but elderly patients should closely observe blood pressure changes when using this product, the initial dose should be small and the dose should be adjusted according to the condition

[Drug Interactions]
(1) In combination with non-depolarizing skeletal muscle relaxants (such as tubocurarine chloride), it may enhance the effect on muscle relaxants.
(2) When enalapril maleate is combined with potassium-sparing diuretics, potassium supplements or potassium-containing substitutes, it can cause an increase in serum potassium, while hydrochlorothiazide reduces blood potassium.
(3) When enalapril maleate is combined with lithium, the concentration of serum lithium is increased; hydrochlorothiazide reduces the renal clearance rate of lithium and increases the risk of lithium poisoning. Therefore, the concentration of lithium should be checked when this product is combined with lithium preparation. In order to avoid high blood lithium.
(4) Non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of diuretics. When combined with this product, blood pressure changes should be observed.
(5) When hydrochlorothiazide is combined with hypoglycemic agents, the dose of hypoglycemic agents should be adjusted.

[Over-Dosage]
Excessive amounts can cause hypotension and should be discontinued immediately. When this product is overdose, it is recommended to take measures including vomiting and/or gavage to correct dehydration, electrolyte imbalance and hypotension through certain steps.

[Pharmacology and Toxicology]

This product is hydrolyzed into an active enalapril (Enalaprilat), which becomes a competitive angiotensin-converting enzyme inhibitor and blocks the conversion of angiotensin I to angiotensin II. To reduce blood pressure. On the other hand, enalapril can slow down the decomposition of bradykinin, lowering vascular resistance, and thus lowering blood pressure.

Hydrochlorothiazide is a diuretic with a mild and long-lasting antihypertensive effect.

Studies have shown that the combination of the two drugs has a synergistic effect, can significantly enhance the antihypertensive effect, and the dose is reduced compared with the single use, can reduce the changes in some blood biochemical parameters that may be caused by diuretics alone.

[Pharmacokinetics]
Oral absorption of enalapril maleate is not affected by food in the gastrointestinal tract. After absorption, it is hydrolyzed in the liver to form dicarboxylic acid type enalapril. After oral administration of enalapril maleate, the peak plasma concentration occurs about 1 hour, and the peak concentration of enalapril appeared 3-4 hours after taking the drug. The effective half-life ($T_{1/2}$) of enalapril after the administration of enalapril maleate is 11 hours, and the antihypertensive effect was maintained for more than 24 hours at the recommended dose. The drug is excreted by the kidney. 94 percent of the oral dose is in the urine and feces with enalapril or enalapril. There are no other metabolites. When the glomerular filtration rate was reduced to less than 30 ml per minute, both the peak time and the steady state time were delayed. Enalapril can be removed by dialysis at a rate of 62 ml per minute. Enalapril do not easily cross the blood-brain barrier. The oral absorption of hydrochlorothiazide is rapid and complete, and the effect occurs in 2 hours, reaching the peak of action in about 4 hours, and the duration of action is about 6-12 hours. The effective half-life ($T_{1/2}$) is 15 hours, and the renal function is prolonged. Hydrochlorothiazide does not have metabolites, but it is rapidly excreted through the kidneys.

[Storage]
Seal and store away from direct sunlight.

[Packaging]
Aluminum-plastic blister packaging, 8 tablets/plate, one plate/carton
Aluminum-plastic blister packaging, 8 tablets/plate, two plates/carton
Aluminum-plastic blister packaging, 8 tablets/plate, three plates/carton

[Shelf-Life]
24 months

[Executive Standard]
National Medical Products Agency Standard YBH254022006-2015Z

[Approval Number]
Guo Yao Zhun Zi H20061313

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